

AN EXAMINATION OF FLUCONAZOLE AND PREVENTION OF SYSTEMIC FUNGAL
INFECTION IN LYMPHOMA A RETROSPECTIVE CHART REVIEW

by
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DNP Capstone Project Approval Form

This is to certify that Michael Johnson
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An Examination of Fluconazole and Prevention of Systemic Fungal Infection in Lymphoma: A Retrospective Chart Review

on August 9, 2018.
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ABSTRACT

Objective: To determine if fluconazole is still effective in preventing fungal infections.

Theoretical Framework: The RE-AIM framework was selected to guide this quality improvement project.

Project Methods: A retrospective chart review of 100 charts were reviewed to determine if patients who received prophylactic fluconazole subsequently acquired invasive fungal infections. Data related to age, serum absolute neutrophil count, and serum albumin levels were planned but only descriptive statistics were used to describe the sample. All of the patients in the sample had active lymphoma diagnoses and were on chemotherapeutic treatment regimens.

Data Analysis: Descriptive statistics including frequency and percentages were used to summarize the data collected related to the sample characteristics of age, type of lymphoma, and neutrophil counts.

Results: Of the 74 charts reviewed there was no patients with positive cultures for an invasive fungal infection, which negated the need for the planned chi-square analysis. Descriptive statistics did not show major differences in demographics

Conclusion: Findings do not prove that fluconazole is the primary reason for the lack of fungal infection. The lack of neutropenia among the sample may be the true reason for lack of fungal infection. Serum albumin levels, or age group also do not have an effect on presence of invasive fungal infection. Patients in this sample were not at a high enough risk for invasive fungal infection based on their acceptable neutrophil counts, which suggests that similar patients can still be used for prophylactic purposes.

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Patients' diagnosed with lymphoma undergo chemotherapy as a part of treatment for their disease. There are many adverse effects related to chemotherapy but perhaps the most dangerous is neutropenia. Neutropenia can be defined as "an absolute neutrophil count (ANC) less than 1500/ μ l; however the risk for infection begins to increase at an ANC less than 1000/ μ l and rises in parallel to a further decrease in neutrophils" (Becker-Cohen et al., 2015). White blood cells are the primary defense against infection in the body. One of the more dangerous infections that can occur due to neutropenia are fungal infections. Fungal infections can mimic both bacterial, and viral infections are often found late (Pagano et al., 2011). Fungal pneumonias such as invasive Aspergillosis have been identified as one of the leading causes of infection related death in immunocompromised patients (Pagano et al., 2011). Age is another risk factor that can increase the risk of infections, especially in those who are immunocompromised. In order to prevent fungal infections from occurring patients are given prophylactic doses of antifungals during the neutropenic phases of their treatment. At a local cancer facility in Buffalo, New York the use of prophylactic antifungal therapy varies between services. The lymphoma service has chosen fluconazole a first generation azole antifungal, while other services such as the leukemia service have decided to use second generation azole antifungals such as posaconazole or voriconazole as their choice for fungal infection prophylaxis. This capstone project is designed to evaluate fluconazole and its effect on systemic fungal infections in active lymphoma patients, as well examine other variables such as age and their correlation to fungal infections.

Invasive fungal infections (IFI) are one of the leading causes of death in patients with malignancy receiving chemotherapy (Sun et al., 2015). This may be due to weakened host defenses secondary to cytotoxic and immunosuppressive agents (Sun et al., 2015). Aspergillosis is especially common in neutropenic patients with infection rates reaching as high as 25% (Oren

& Paul, 2014). Incidence of IFI was examined and found that 407 episodes (8.3%) of 4,889 chemotherapy courses included the presence of IFI (Sun et al., 2015). The incidence of IFI was also found to be in highest in older age populations (Sun et al., 2015). The increased risk of infection in older adults may be due to alterations in the functioning and development of B cells and T cells (Shaw, Goldstein, & Montgomery, 2013). In the elderly adult activation of the innate immune system results in dysregulated inflammation, resulting in impaired ability to mount immune responses (Shaw et al., 2013). Presence of infection in lymphoma patient's can be a predictor of death making prevention key to surviving the disease (Dendle et al., 2017). An examination of 325 lymphoma patients showed that 63% of the patients experienced an infectious episode during their treatment 19% of those infections were fungal infections (Dendle et al., 2017). A strategy identified to help prevent infection in lymphoma patients was using antimicrobial prophylaxis (Dendle et al., 2017). Antifungal prophylaxis has been shown to reduce mortality among immune compromised patient's especially those undergoing chemotherapy.

Problem Identification

The use of first generation azole antifungal medications prophylactically have been the gold standard in prevention of systemic fungal infections in neutropenic infections. Systematic reviews have shown that fluconazole the most often used antifungal for prophylaxis is effective in prevention of fungal infections, with a low side effect profile (Gotsche & Johansen, 2014). Fluconazole was also found to be very effective in prevention of invasive aspergillosis, one of the more common and deadly fungal infections (Ping, Zhu, Gao, Yue, & Wu, 2013).

Since the development of second generation antifungals the use of fluconazole for fungal prophylaxis has decreased. The lymphoma service however still continues to prescribe

fluconazole instead of switching to the second generation therapy. Discussion with the lymphoma team has determined that there is a gap in practice. The service continues to use fluconazole based on older evidence, that was presented prior to the evaluation of second generation antifungals. The APNs are especially curious as to why their prescribing practices have not changed due to new evidenced based practice. The lead Attending of the lymphoma service wants to determine if their current therapy still continues to be effective despite further evidence to support the use of second generation azole antifungals. He believes that there is still a profound lack of systemic fungal infection prevention that occurs when patient's take fluconazole. He also believes that fluconazole has less medication interactions. The objectives of this capstone project are to evaluate the rate of fungal infections in active lymphoma patients, and determine if fluconazole decreases the rate of infection in lymphoma patient's receiving chemotherapy. Data will be collected by conducting a randomized chart review. The results of the data are going to be utilized by the lymphoma service to help determine the future of their prescribing practices. It may also be provided to other services in the facility to result in a change in prescribing practice.

Literature Review

A systematic literature review was conducted. Databases that were searched include Cochrane Database of Systematic Reviews, MEDLINE, and PubMed. The key words are *fungal infection, prophylactic antifungal, fluconazole, cancer, immune compromised, elderly, infection, and neutropenia*. The literature review included articles from 2008 through 2017 and were limited to academic journals, and systematic reviews. Articles were excluded if they were not from peer reviewed academic journals, or systematic reviews. The references from key articles were also reviewed and selected articles were retrieved. After review of the literature the

following themes organized the literature review: incidence of fungal infections, impact of age on rate of infection, general antifungal use for fungal infection prevention with comparison of effectiveness and comparison of different classes of antifungals.

Incidence of Fungal Infections

Fungal infections are opportunistic infections and are contracted due to specific risk factors (Pagano et al., 2011). A risk assessment was completed to examine the largest risks of contraction of fungal infections. Risks included genetics, environmental, and malfunction of immune system (Pagano et al., 2011). Fungal infections related to the immune system most commonly occur due to neutropenia, and impaired cell immunity (Pagano et al., 2011). Neutrophils and their role against fungal infections are crucial for prevention of infection of the disease (Pagano et al., 2011). Neutropenia is associated largely with those who have malignancy, specifically leukemia and lymphoma patients (Pagano et al., 2011). Besides neutropenia risk for IFI also increases with use of steroids, and antivirals (Pagano et al., 2011). These combinations are frequently used with chemotherapy regimens placing those with malignancy at an extremely high risk.

IFI is one of the leading causes of death in patients with malignancy receiving chemotherapy due to impaired host defense systems (Sun et al., 2015). One of the deadliest infections occurs with *Aspergillus* spp. (Sun et al., 2015). An examination of a population of patients across 35 hospitals was completed to examine the incidence of fungal infection (Sun et al., 2015). A total of 4,192 patients were included in the population and received 4,889 course of chemotherapy (Sun et al., 2015). The results showed that there were 407 (8.3%) of cases that experienced IFI with 12 (8.2%) mortality from IFI (Sun et al., 2015). The presence of IFI was also found to be higher in older populations greater than 60 years (Sun et al., 2015). Other factors

associated with IFI were neutropenia with an ANC <500, decreased serum albumin, and previous IFI (Sun et al., 2015). A total of 1,211 (24.8%) of patients were treated with antifungal agents during chemotherapy, which included 827 (13.4%) treated with antifungal prophylaxis (Sun et al., 2015). Around 48.4% of those receiving prophylaxis were given doses of fluconazole (Sun et al., 2015). Overall the results of the study suggested use of antifungal prophylaxis especially patients that are identified as high risk (Sun et al., 2015). The antifungal of choice for this study was fluconazole, though there was still 2.7% of IFI with patients who did take prophylactic fluconazole (Sun et al., 2015). The researchers suggest that perhaps fluconazole is not the best first choice for prophylaxis and that a second generation azole such as posaconazole should be considered (Sun et al., 2015).

The incidence of IFI has reached as high as 12% with 7.9% due to *Aspergillus* (Nosari et al., 2014). Multiple studies have been conducted to examine leukemia's and incidence of IFI, with a profound lack of focus on lymphoproliferative disorders (Nosari et al., 2014). A study retrospectively examined IFI and lymphoproliferative disorders such as chronic lymphocytic leukemia, Hodgkin and non-Hodgkin lymphoma, multiple myeloma, and hairy cell leukemia (Nosari et al., 2014). Lymphoproliferative disorders also cause the patient to have severe neutropenia and immunosuppression due to the disease itself as well as the advancing therapies used to treat the disease (Nosari et al., 2014). Records of 1,355 patients with lymphoproliferative disorders were reviewed with the identification of 42 patients (3.3%) with IFI (Nosari et al., 2014). The diagnosis of IFI however proved to be very difficult in this study due to the lack of reliability on blood cultures (Nosari et al., 2014). This however led to the realization that rapid initiation of antifungals for reduction in mortality despite the immunosuppression (Nosari et al., 2014).

Diffuse large B cell lymphoma is one of the most common histological subtypes of lymphoma (Dendle et al., 2017). Treatment usually consists of chemotherapy with agents such as rituximab, cyclophosphamide, doxorubicin, vincristine as well as steroid therapy (Dendle et al., 2017). Neutropenia occurs in 10 to 20% of patients being treated for lymphoma resulting in an increased risk of infection (Dendle et al., 2017). Infection was found to be a common among B-cell lymphoma patients with about 63% of patients experiencing one infection within their course of therapy (Dendle et al., 2017). Fungal infections accounted for 19.2% of the reported infections (Dendle et al., 2017). Other factors that led to increased risk include age greater than 65, and a Charlson comorbidity score greater than 3 (Dendle et al., 2017). This study concluded that prevention of infection is the best way to prevent mortality in patients with B cell lymphoma (Dendle et al., 2017). Recommended prevention strategies include patient education, vaccination, and antimicrobial prophylaxis (Dendle et al., 2017).

Age and Infection

A majority of studies focusing on the incidence of infection and risk factors always include age as a potential for heightened risk. Elderly populations specifically are more at risk of infections, without the added complication of neutropenia. A decrease in immune function in the elderly is due to a dysregulation of the immune system (Shaw et al., 2013). As the body ages the adaptive immune system composed of B cells and T cells become altered rendering them weak against infectious pathogens (Shaw et al., 2013). The innate immune system also experiences changes over time resulting in dysregulated inflammation and impaired ability to mount an efficient immune response (Shaw et al., 2013). The size of the innate immune cell population has also been found to decrease during age (Shaw et al., 2013). Though it is not significant enough to cause neutropenia, neutrophilia has been found to be a major risk factor for death in aged adults.

Neutrophil movement is also altered in older aged adults (Shaw et al., 2013). Chemotaxis is defined as the movement of neutrophils to the site of infection (Shaw et al., 2013). Chemotaxis in the elderly has been found to be diminished reducing the migration of neutrophils to the inflamed tissue (Shaw et al., 2013). With the decrease in innate immunity causing problems with neutrophils the added complication of malignancy would place elderly patients at a high risk for IFI (Shaw et al., 2013). Antifungal prophylaxis is a major requirement to ensure that the older population does not develop fungal infections.

Antifungal Use and Efficacy

Incidence of fungal infection is prevalent in those with malignancy especially lymphoma patients who experience severe neutropenia due to chemotherapy. The majority of the studies found highlight prophylaxis as the best way to prevent IFI, though selection of the best agent is to be determined. First generation azole antifungals such as fluconazole have been the standard of prophylactic treatment, however the development of second generation azole antifungals have shifted practice towards antifungals such as posaconazole and Voriconazole. A systematic review was conducted to compare first and second generation azole antifungals to determine if there is more evidence to support the use of second generation azole antifungals for IFI prophylaxis (Ping et al., 2013). First generation azole antifungals have been widely used because they are available in both oral and IV preparations, have a low toxicity profile, and few adverse effects (Ping et al., 2013). The overwhelming use of first generation antifungals had led to resistant pathogens, which warranted the development of second generation antifungals (Ping et al., 2013). Second generation antifungals also show a lower toxicity profile and have been shown to have high levels of activity against resistant pathogens (Ping et al., 2013). The result of four trials involving the use of second generation antifungals significantly reduced probable IFI

compared with first generation agents (Ping et al., 2013). When examining specific drugs posaconazole showed the largest difference in reduced IFI (Ping et al., 2013). Voriconazole and posaconazole also decreased the cases of invasive aspergillosis (Ping et al., 2013). The use of fluconazole however also showed a reduction in morbidity and mortality, especially in those who received an allogeneic stem cell transplant and populations experiencing prolonged neutropenia (Ping et al., 2013). Fluconazole was found to have a low adverse effect profile but lacks efficacy against molds (Ping et al., 2013).

A mixed treatment comparison examining first and second generation antifungals was also used to help determine optimal antifungal prophylaxis. The results again show that the second generation azole antifungals specifically posaconazole was more effective in the prevention of IFI in comparison to fluconazole (Pechlivanoglou, Le, Daenen, Snowden, & Postma, 2014). The comparison study also examined azole agents and their effectiveness against invasive aspergillosis. Using posaconazole or voriconazole for invasive aspergillosis again proved to be more effective than fluconazole (Pechlivanoglou et al., 2014).

Risk classification was assigned to different malignancies to help better determine the risk of IFI. High risk clinical examples included Acute Leukemia, and allogeneic stem cell transplants (Pagano et al., 2011). Lower risk examples included patients receiving dose escalated chemotherapy for lymphoma (Pagano et al., 2011). Very low risk included chronic myeloid leukemia. Recommend treatments for antifungal prophylaxis were then assigned to each classification (Pagano et al., 2011). The best recommended prophylactic medication for high risk was posaconazole due to its broad spectrum, ability to protect against mold and low incidence of IFI (Pagano et al., 2011). Fluconazole was assigned to be a secondary drug of choice for low risk patients due to its lack of treating specific molds and risk of resistance (Pagano et al., 2011).

A detailed examination of the literature shows the incidence of fungal infections is increased especially in the elderly, and immune compromised due to malignancy. Chronic states of neutropenia, which occur in lymphoma and leukemia patient's place these populations at high risk. Aspergillosis is one of the deadliest and most common IFI's for immune suppressed patients to contract. The simplest way to prevent IFI's from occurring is the use of prophylactic antifungals. There is an overwhelming amount of evidence supporting the use of second generation azole antifungals such as posaconazole and voriconazole. These drugs are found to have a large spectrum, with low toxicity profiles. The continued use of fluconazole is still seen as effective but increases the risk of resistant organism infection. Further examination of the use of fluconazole prophylactically and it efficacy against IFI's will be analyzed in active lymphoma patient's undergoing chemotherapy.

Theoretical Framework

The selected framework that can be used for this capstone project is the RE-AIM model which, is defined as reach, efficacy, adoption, implementation, and maintenance (Jeong, Jo, Oh, & Oh, 2015). This model focuses on the impact of an intervention on both the individual and organizational levels (Jeong et al., 2015). The Individual dimensions include reach, efficacy, and maintenance (Jeong et al., 2015). Organizational models include adoption, implementation, and maintenance (Jeong et al., 2015). Each piece of the RE-AIM framework can be applied to the use of prophylactic fluconazole to prevent IFI. The reach determines the amount of the target population that is involved with intervention (Jeong et al., 2015). Reach in IFI prevention are those diagnosed with active lymphoma taking prophylactic fluconazole. Efficacy is the success of the intervention (Jeong et al., 2015). The lack of systemic fungal infections due to the use of fluconazole is the effect and considered a positive effect. Adoption includes the settings that

accepts the intervention (Jeong et al., 2015). The lymphoma clinic has adopted the intervention of administering fluconazole prophylactically to patients getting chemotherapy. Implementation is the extent to which the intervention is used (Jeong et al., 2015). The use of fluconazole is a gold standard in the lymphoma clinic and is given to patients who are undergoing chemotherapy and will experience neutropenia. Finally, maintenance is the length of time the intervention is sustained (Jeong et al., 2015). The use of fluconazole for prevention of systemic fungal infections has been used for an extremely long period and continues to be used. It is considered a gold standard therapy in the Lymphoma department, yet current evidence does not suggest its use for patient who are commonly neutropenic. By applying the RE-AIM framework, the current prescribing practice of fluconazole can be evaluated. A full data collection and analysis will help determine the need for further program evaluation, and practice change based on current evidence based recommendations.

Design and Methods

In order to properly evaluate the effectiveness of fluconazole and the rate of IFI a retrospective chart review with accompanying analysis was completed. The chart review took place at a local oncology facility in Western New York. The population being sampled were those with active lymphoma. Charts were reviewed between the years 2012 to 2017. Criteria for selection includes adult patients ages 20 to 99, have an active case of lymphoma are receiving chemotherapy treatment, and are receiving fluconazole prophylaxis. Exclusion criteria includes, those without a lymphoma diagnosis, pediatric patients, and those with allergies to fluconazole. The total number of 100 charts were selected. Descriptive statistics were then run to determine the distribution of ages.

Data Analysis

After data were collected and organized it was transferred to IBM SPSS data processing software for data analysis. The two primary variables being analyzed were presence of invasive fungal infection as the dependent variable, and administration of fluconazole as the independent variable. Bivariate descriptive statistics were completed in order to provide details on the sample selected. A contingency table was planned to cross-tabulate data related to IFI and prescription of fluconazole. However, this analysis was not completed because there was not a single case of fungal infection present in the sample data collected.

A chi-square analysis on fluconazole and presence of invasive fungal infection several were to be performed on other variables that may contribute to IFI but were not completed due to the lack of IFI in the sample. The ages of patients were grouped into three categories young age, middle age, and old age and were to be compared to presence of IFI. An analysis on ANC with grouping related to neutrophil levels was planned but not conducted due to the lack of IFI. The use of descriptive statistics alone was used to help explain the lack of IFI.

Results

The total population provided for chart review was 435 participants that had received high dose chemotherapy with fluconazole prophylaxis in the last 5 years. The population was provided via excel spreadsheet and randomized by number. The sample of 100 charts was then examined and data was extracted based on the inclusion and exclusion criteria. The final sample included 74 charts which, had data extracted for final analysis. The remaining 26 charts were excluded due to either the patient not be diagnosed with lymphoma (actual diagnosis was CLL), and those who were provided with a treatment plan but decided to seek a second opinion.

Descriptive statistics showed a well balanced sample selected from the total population. The mean age of the sample was 57.31 [Table 1], with 59 percent of the sample being male. The age ranges of the sample were separated into three age groupings (young age, middle age, and old age) the frequency was about even for all three ages (25,26, and 23 respectively) [Table 2]. The most common diagnosis for the sample was diffuse large b-cell (DLBCL) making up 71.6 percent of the total sample [Table 3] which, follows the literature for being the most common diagnosed form of lymphoma and is. The average of the mean serum ANC values was 5.86 with a minimum value of 1.52 and maximum value of 19.19 [Table 1]. In general, the sample was not considered neutropenic throughout their chemotherapy treatment because it falls within the range of normal serum ANC levels. The average of mean serum albumin values was 3.71 with a minimum of 2.5 and maximum of 5.16 [Table 1] the sample on average was still within the normal limits of serum albumin levels.

There was not a single patient in the sample that was diagnosed with any type of fungal infection. Due to the overwhelming lack of fungal infection present there was no need to calculate a cross tabulation, as well as a chi-square analysis because the total lack of a fungal infection was proven via data collection.

Table 1

General Characteristics of Sample (N=74)

Characteristic	N	Minimum	Maximum	Mean	Std. Deviation
Age	74	20	82	57.31	15.773
Number Cycles	74	1.0	9.0	4.584	1.7897
Mean Serum ANC	74	1.52	19.19	5.6896	3.21850
Mean Serum Albumin	74	2.50	5.16	3.7176	.60671

Note. ANC= Absolute Neutrophil Count

Table 2

Age Ranges

Range		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Young Age	25	33.8	33.8	33.8
	Middle Age	26	35.1	35.1	68.9
	Old Age	23	31.1	31.1	100.0
	Total	74	100.0	100.0	

Table 3

Lymphoma Diagnosis Frequency (N=74)

Diagnosis		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	DLBCL	53	71.6	71.6	71.6
	Mantle	4	5.4	5.4	77.0
	Hodgkin's	8	10.8	10.8	87.8
	T-Cell	3	4.1	4.1	91.9
	CLL	2	2.7	2.7	94.6
	Grey Zone	2	2.7	2.7	97.3
	Large Cell	1	1.4	1.4	98.6
	Composite	1	1.4	1.4	100.0
	Total	74	100.0	100.0	

Note. DLBCL= Diffuse Large B-Cell

Discussion

It cannot be deduced that fluconazole in this study is the primary reason for the lack of fungal infection in this sample of lymphoma patients. The primary factor that may play a role in the lack of fungal infections in lymphoma patients are their ANC values. Unlike the leukemia patient's who experience profound neutropenia throughout their total treatment the lymphoma patient's rarely reach a state of profound neutropenia. The data collected shows that even the minimum value collected for mean ANC is still within range for normal serum ANC values. Since the sample wasn't truly neutropenic they aren't at as high of a risk for invasive fungal infections, warranting the use of a secondary agent like fluconazole. Lymphoma patient's can be placed into the low risk neutropenic category due to the lack of depth and length of neutropenia. The depth of neutropenia was 1.52 (the minimum value), which is still above the level of neutropenia. Since the overall average of the sample was also above the level of neutropenia it can be deduced that the length of time a lymphoma patient is neutropenic is short. The recommendation for low risk patient's for prophylaxis is the use of fluconazole (Pagano et al., 2011).

Similarly, with the mean ANC values serum albumin values also had a mean value within the normal limits. Therefore, again serum albumin could also not prove to be a contributory factor for the prevention of invasive fungal infection. Examination of age ranges also yields the same result. There was no correlation between the age of the patient and the presence of fungal infection, despite the evidence showing a higher risk for infection as the age increases.

Ethical Issues and Protection of Human Subjects

The development of this capstone proposal has been a culmination of selected data from various journals and institutes to build a case for potential gaps found in research. The lead

attending for the lymphoma service at the selected oncology facility has authorized research to be completed on past patients to allow for a potential change in prescribing practices. I do not own the rights to the studies selected in the literature review, and use them purely as reference to help present the need for this capstone project. There is no conflict of interest being presented with this capstone project as it is being completed as part of the Doctorate of Nursing practice curriculum requirement. This data will be presented to both the University at Buffalo, as well as Roswell Park Cancer Institute. There will be no financial gain after the completion of the capstone project, and the data extracted from medical charts received will remain property of Roswell Park Cancer Institute.

In regards to protection of human subjects there will be no physical interaction with subjects, instead their medical records will be accessed. In order to minimize the risk to human subjects the capstone proposal will be submitted for International Review Board (IRB) approval prior to initiation of research. Review of medical record data will involve minimal risk without the identification of the subjects in the data extraction or analysis. Data extracted will not violate the privacy of subjects provided for chart review, and will maintain strict confidentiality between the student and the medical data provided. The information extracted from medical records will be in compliance with the Health Insurance Portability and Accountability Act (HIPPA). Health identifiers will be removed from data extraction leaving only basic information such as age, gender, and lymphoma diagnosis to be used for data analysis. The use of private health indicators such as medical record number, social security number, or name will not be included in any data removed from the medical record. This capstone project will follow accordance of both IRB standards as well the federal HIPPA regulations.

Limitations

The primary limitation for this study would be time needed for completion. Since this was completed as part of the capstone requirement there was a profound lack of time needed to complete a thorough examination to determine if fluconazole is effective in preventing fungal infections. The sample size could have also been increased, and even possibly encompassed the entire population provided by the institute, but again was limited due to the time available to complete the study. The study also only took place at a single cancer institute. Sample data could have been collected from other cancer facilities to help examine a wider population of lymphoma patients. The lack of a research team can also be seen as a major limitation. As the only person completing this study a team that would help collect data, as well as check data collected could have been better to ensure no errors were recorded in the data as well as to increase efficiency of the study completion. Finally, the most important limitation to this study would be the lack of experience of the student.

Conclusion

The results of this capstone project were not expected to be as direct as they were. There was some expectation that fungal infection would be present in the lymphoma population. Prior experience by this student has seen lymphoma patient's with severely neutropenic levels, placing them at a very high risk for invasive fungal infections. Since the prior experience has only taken place in the inpatient setting there was a lack of how the total ANC values may look for a lymphoma patient undergoing treatment.

The profound lack of fungal infection means that there is not a need for a change in prescribing practice. The sample selected is not at a high enough risk for fungal infection due to the lack of neutropenia, and therefore current practice with prophylactic fluconazole, and

frequent lab work monitoring can continue to occur to help with prevention of invasive fungal infections.

References

- Becker-Cohen, R., Ben-Shalom, E., Rinat, C., Feinstein, S., Geylis, M., & Frishberg, Y. (2015). Severe neutropenia in children after renal transplantation: incidence, course, and treatment with granulocyte colony-stimulating factor. *Pediatric Nephrology*, *30*(11), 2029-2036. doi:10.1007/s00467-015-3113-7
- Dendle, C., Gilbertson, M., Spelman, T., Stuart, R. L., Korman, T. M., Thursky, K., . . . McQuilten, Z. (2017). Infection is an Independent Predictor of Death in Diffuse Large B Cell Lymphoma. *SCIENTIFIC REPORTS*, *7*, 1. doi:10.1038/s41598-017-04495-x
- Gotzsche, P. C., & Johansen, H. K. (2014). Routine versus selective antifungal administration for control of fungal infections in patients with cancer. *COCHRANE DATABASE OF SYSTEMATIC REVIEWS*, *9*;2017;(9), CD000026. doi:10.1002/14651858.CD000026.pub2
- Jeong, H.-J., Jo, H.-S., Oh, M.-K., & Oh, H.-W. (2015). Applying the RE-AIM Framework to Evaluate the Dissemination and Implementation of Clinical Practice Guidelines for Sexually Transmitted Infections. *Journal of Korean Medical Science*, *30*(7), 847-852. doi:10.3346/jkms.2015.30.7.847
- Nosari, A. M., Pioltelli, M. L., Riva, M., Marbello, L., Nichelatti, M., Greco, A., . . . Morra, E. (2014). Invasive fungal infections in lymphoproliferative disorders: a monocentric retrospective experience. *Leukemia & Lymphoma*, *55*(8), 1844-1848. doi:10.3109/10428194.2013.853299
- Oren, I., & Paul, M. (2014). Up to date epidemiology, diagnosis and management of invasive fungal infections. *Clinical Microbiology and Infection*, *20*(6), 1-4. doi:10.1111/1469-0691.12642

- Pagano, L., Akova, M., Dimopoulos, G., Herbrecht, R., Drgona, L., & Blijlevens, N. (2011). Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. *Journal of Antimicrobial Chemotherapy*, *66*(suppl_1), i5-i14. doi:10.1093/jac/dkq437
- Pechlivanoglou, P., Le, H. H., Daenen, S., Snowden, J. A., & Postma, M. J. (2014). Mixed treatment comparison of prophylaxis against invasive fungal infections in neutropenic patients receiving therapy for haematological malignancies: A systematic review. *Journal of Antimicrobial Chemotherapy*, *69*(1), 1-11. doi:10.1093/jac/dkt329
- Ping, B., Zhu, Y., Gao, Y., Yue, C., & Wu, B. (2013). Second- versus first-generation azoles for antifungal prophylaxis in hematology patients: a systematic review and meta-analysis. *Annals of Hematology*, *92*(6), 831-839. doi:10.1007/s00277-013-1693-5
- Shaw, A. C., Goldstein, D. R., & Montgomery, R. R. (2013). Age-dependent dysregulation of innate immunity. *Nature Reviews Immunology*, *13*, 875+.
- Sun, Y., Huang, H., Chen, J., Li, J., Ma, J., Li, J., . . . Huang, X. (2015). Invasive fungal infection in patients receiving chemotherapy for hematological malignancy: a multicenter, prospective, observational study in China. *Tumor Biology*, *36*(2), 757-767. doi:10.1007/s13277-014-2649-7



University at Buffalo Institutional Review Board (UBIRB)

Office of Research Compliance | Clinical and Translational Research Center Room 5018

875 Ellicott St. | Buffalo, NY 14203

UB Federalwide Assurance ID#: FWA00008824

May 16, 2018

Dear [Michael Johnson](#):

On 5/16/2018, the IRB reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	An Examination of Fluconazole and Prevention of Systemic Fungal Infection in Lymphoma a Retrospective Chart Review
Investigator:	Michael Johnson
IRB ID:	STUDY00002523
Funding:	None
Grant ID:	None
IND, IDE, or HDE:	None
Documents Reviewed:	<ul style="list-style-type: none"> • Johnson HIPAA-Waiver.docx, Category: Other; • Johnson IRB Submission, Category: IRB Protocol; • Johnson Capstone Data Collection Form.xlsx, Category: Other;

The IRB approved the study from 5/16/2018 to 5/15/2019 inclusive. Before 5/15/2019 or within 30 days of study closure, whichever is earlier, you are to submit a continuing review with required explanations. You can submit a continuing review by navigating to the active study and clicking Create Modification / CR.

If continuing review approval is not granted before the expiration date of 5/15/2019, approval of this study expires on that date. The Initial Study materials for the project referenced above were reviewed and approved by the SUNY University at Buffalo IRB (UBIRB) by Initial Study Review. Before to 5/15/2019 inclusive. Before 5/15/2019 or within 30 days of study closure, whichever is earlier, you are to submit a continuing review with required explanations. You can submit a continuing review by navigating to the active study and clicking Create Modification / CR.

If continuing review approval is not granted before the expiration date of 5/15/2019, approval of this study expires on that date. or within 30 days of study closure, whichever is earlier, you are to submit a continuing review application with required explanations. You can submit a

continuing review application by navigating to the active study in Click IRB and clicking Create Modification / Continuing Review. Studies cannot be conducted beyond the expiration date without re-approval by the UBIRB.

In conducting this study, you are required to follow the requirements listed in the Investigator Manual (HRP-103), which can be found by navigating to the IRB Library within the IRB system.

HIPAA Partial Waiver granted for Recruitment

The UBIRB has approved the HIPAA Partial Waiver to permit you to receive personal health information as specified in section (1). The Partial Waiver Form has met the required elements of the federal regulations of HIPAA.

UB IRB approval is given with the understanding that the most recently approved procedures will be followed and the most recently approved consenting documents will be used. If modifications are needed, those changes may not be initiated until such modifications have been submitted to the UBIRB for review and have been granted approval.

Prior to the expiration of this approval, you will receive notification that it is time for the UBIRB to conduct its periodic review of your study. Studies cannot be conducted beyond expiration date without re-approval by the UBIRB.

As principal investigator for this study involving human participants, you have responsibilities to the SUNY University at Buffalo IRB (UBIRB) as follows:

1. Ensuring that no subjects are enrolled prior to the IRB approval date.
2. Ensuring that the study is not conducted beyond the expiration date without re-approval by the UBIRB.
3. Ensuring that the UBIRB is notified of:
 - All Reportable Information in accordance with the Reportable New Information Form Smart Form.
 - Project closure/completion by the Continuing Review/Modification/ Study Closure smart form.
4. Ensuring that the protocol is followed as approved by UBIRB unless a protocol amendment is prospectively approved.
5. Ensuring that changes in research procedures, recruitment or consent processes are not initiated without prior UBIRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects.
6. Ensuring that the study is conducted in compliance with all UBIRB decisions, conditions, and requirements.

7. Bearing responsibility for all actions of the staff and sub-investigators with regard to the protocol.

8. Bearing responsibility for securing any other required approvals before research begins.

If you have any questions, please contact the UBIRB at 716-888-4888 or ub-irb@buffalo.edu.

EXAMINATION OF FLUCONAZOLE AND THE
PREVENTION OF SYSTEMIC FUNGAL
INFECTION IN LYMPHOMA: A
RETROSPECTIVE CHART REVIEW

Michael Johnson
Spring 2018

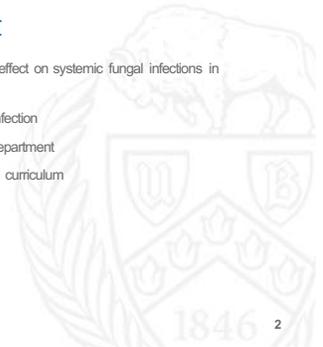
University at Buffalo
School of Nursing



University at Buffalo
School of Nursing

Purpose of this Capstone Project

- This capstone project is designed to evaluate fluconazole and its effect on systemic fungal infections in active lymphoma patients
- Examine a potential connection between age and rate of fungal infection
- Determine the future of prescribing practices in the Lymphoma department
- Fulfill the requirements of the Doctorate of Nursing Practice (DNP) curriculum



University at Buffalo
School of Nursing

PICO Question

- Does the use of fluconazole or age influence the rate of fungal infections in patients who have active lymphoma receiving chemotherapy?



University at Buffalo
School of Nursing

Risks for Fungal Infections

- Malignancy
- Chemotherapy induced neutropenia
- Steroid use
- Antiviral use
- Increasing age

(Pagano et al., 2011)



Neutropenia and Fungal Infections

- Neutropenia can be defined as “an absolute neutrophil count (ANC) less than 1500/ μ l” (Becker-Cohen et al., 2015).
- A lack of neutrophils allows opportunistic infections to occur, one of which are invasive fungal infections (IFI).
- Fungal pneumonias have been identified as one of the leading causes of infection related death in immunocompromised patients (Pagano et al., 2011).
- In order to prevent fungal infections from occurring patients are given prophylactic doses of antifungals.

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Incidence of Fungal Infections

- Incidence of IFI has reached as high as 12% for those with malignancy, with 7.9% due to invasive *Aspergillus spp.* (Nosari et al., 2014).
- Fungal infections accounted for 19.2% of reported infections in a study examining B-cell lymphoma (Dendle et al., 2017).
- Out of a sample of 4,883 patients receiving chemotherapy, 8.3% of the cases experienced IFI, while another 8.2% of the cases had died due to IFI (Sun et al., 2015).

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Age and Infection Risk

- Dysregulation of the immune system occurs as the body ages.
- Adaptive immune system becomes altered rendering the cells weak against infectious pathogens.
- Innate immune system experiences dysfunctional inflammation and impaired ability to mount an effective immune response.
- Size of the innate immune system decreases as the body ages
- Diminished chemotaxis occurs

(Shaw et al., 2013)

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Prevention of Fungal Infection

- Consensus of studies is that prophylaxis as the best way to prevent IFI
- Selection of agent is under debate but favors second generation
- Two classifications:
 - First generation antifungals- Fluconazole
 - Second generation antifungals- Posaconazole, and Voriconazole

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Advantages and Disadvantages of First Generation Antifungals

- Advantages:
 - Widely used
 - Oral and Intravenous (IV) preparations
 - Low toxicity profile
 - Few Adverse Effects
- Disadvantages:
 - Overuse has led to resistant pathogens
 - Not a large mold spectrum of coverage

(Ping et al., 2013)



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Advantages and Disadvantages of Second Generation Antifungals

- Advantages:
 - Large spectrum including mold coverage
 - Low toxicity
 - Few Adverse Effects
- Disadvantages:
 - More expensive than first generation
 - Interacts with numerous chemotherapy agents

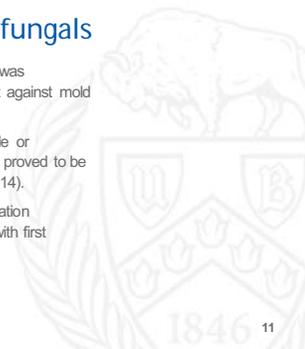
(Ping et al., 2013)



10

First Vs. Second Generation Antifungals

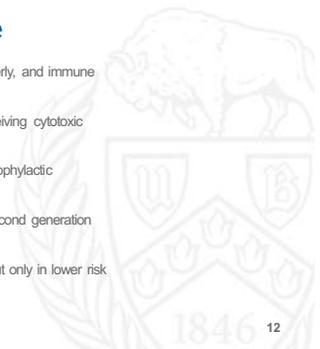
- Best recommended prophylactic medication for high risk was posaconazole due to its broad spectrum, ability to protect against mold and low incidence of IFI (Pagano et al., 2011).
- A mixed treatment comparison revealed that posaconazole or voriconazole used for prevention of invasive aspergillosis proved to be more effective than fluconazole (Pechlivanoglou et al., 2014).
- The result of four trials involving the use of second generation antifungals significantly reduced probable IFI compared with first generation agents (Ping et al., 2013)



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Summary of Presented Evidence

- Incidence of fungal infections is increased especially in the elderly, and immune compromised due to malignancy.
- Chronic states of neutropenia, which can occur in patient's receiving cytotoxic chemotherapy significantly increase the risk for IFI.
- The easiest way to prevent IFI's from occurring is the use of prophylactic antifungals.
- An overwhelming amount of evidence supporting the use of second generation azole antifungals such as posaconazole and voriconazole
- Continued use of fluconazole has been found to be effective but only in lower risk patient's.



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RE-AIM Model

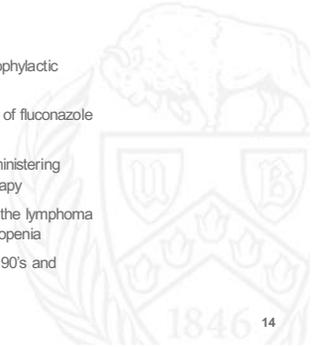
- Defined as **Reach, Efficacy, Adoption, Implementation, and Maintenance** (Jeong et al., 2015)
- The model focuses on the impact of an intervention on both the individual and organizational levels
- Individual Level:
 - Reach
 - Efficacy
 - Maintenance
- Organizational Level:
 - Adoption
 - Implementation
 - Maintenance



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RE-AIM Model Applied

- **Reach**- those diagnosed with active lymphoma taking prophylactic fluconazole.
- **Efficacy**- lack of systemic fungal infections due to the use of fluconazole (a positive effect).
- **Adoption**- lymphoma clinic utilizes the intervention of administering fluconazole prophylactically to patients getting chemotherapy
- **Implementation**- use of fluconazole is a gold standard in the lymphoma clinic for those undergoing chemotherapy at risk for neutropenia
- **Maintenance**- fluconazole has been used since the early 90's and continues to be used despite new evidence.



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Contribution to Clinical Practice

- Determine the need for a change in clinical practice
- Improve prescribing practices
- Apply evidence based practices to advanced nursing practice
- UB SON Outcomes:
 - 1, 3, 4, 5, 6, 9, & 10
- Essentials of Doctoral Education for Advanced Nursing Practice:
 - I, II, III, VI, VII, & VIII



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Methodology

- A retrospective chart review was completed
- Charts were reviewed from the Lymphoma department at a local oncology Facility
- Sample= 100 charts
- Inclusion criteria- ages 20-99, active lymphoma, receiving fluconazole
- Exclusion criteria- pediatric patients, have intolerance or allergy to fluconazole, and are not a lymphoma patient



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Data Collection

- Data were extracted and organized on an excel spreadsheet
- Extracted data included age (measured in years only), gender, lymphoma diagnosis, presence of fungal infection, mean ANC, and mean serum albumin.
- Ages were grouped into three categories:
 - Young adult (20-40 years old)
 - Middle-age adult (40-64 years old)
 - Older adult (65 and older)
- Mean ANC was calculated for all total cycles of treatment per patient
- Mean Albumin was calculated for all total cycles of treatment per patient

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Data Analysis

- Primary independent variable is the prescribing of fluconazole
- Dependent variable is the presence of fungal infection
- Data collected were coded and entered into SPSS Statistics for analysis
- Descriptive statistics for all data groups were processed
- Bivariate descriptive statistics were to be performed via crosstabulation followed by a chi-square analysis, however the absence of fungal infections did not require further analysis
- Crosstabulation and chi-square analysis by age groupings, ANC groupings, and serum albumin groups were planned but unnecessary due to the absence of IFI.

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Sample Statistics

- Total population was 435 patient's
- Randomized selection of 100 charts for sample reviewed
 - 74 charts included in final analysis
 - 26 charts excluded
 - 22 excluded due to lack of lymphoma diagnosis (transferred to leukemia service with diagnosis of CLL)
 - 4 treatment plan in place, but did not pursue treatment and received second opinion

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Results

Table 1
General Characteristics of Sample (N=74)

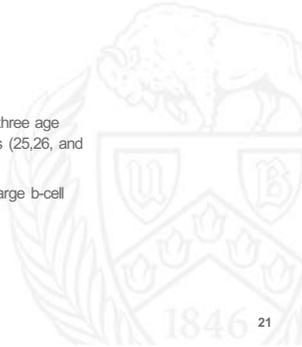
Characteristic	N	Minimum	Maximum	Mean	Std. Deviation
Age	74	20	82	57.31	15.773
Number Cycles	74	1.0	9.0	4.584	1.7897
Mean Serum ANC	74	1.52	19.19	5.6896	3.21850
Mean Serum Albumin	74	2.50	5.16	3.7176	.60671
Age Ranges	74	1	3	1.97	.810
Valid N	74				

Note. ANC= Absolute Neutrophil Count

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Overview of Results

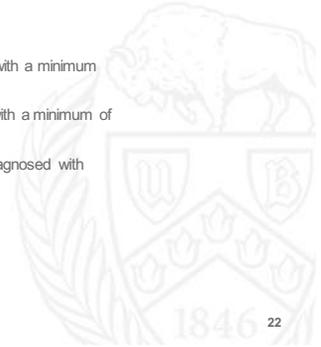
- The mean age of the sample was 57.31
- 59 percent of the sample was male.
- When the age ranges of the sample were separated into three age groupings the frequency was about even for all three ages (25,26, and 23 respectively).
- The most common diagnosis for the sample was diffuse large b-cell (DLBCL) making up 71.6 percent of the total sample.



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Overview of Results

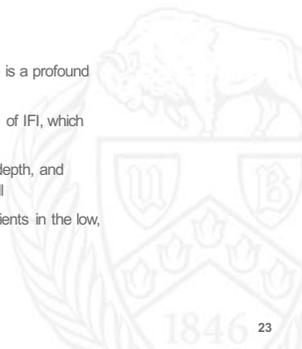
- The average of the mean serum ANC values was 5.86 with a minimum value of 1.52 and maximum value of 19.19.
- The average of mean serum albumin values was 3.71 with a minimum of 2.5 and maximum of 5.16
- There was not a single patient in the sample that was diagnosed with any type of fungal infection.



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Why the lack of IFI?

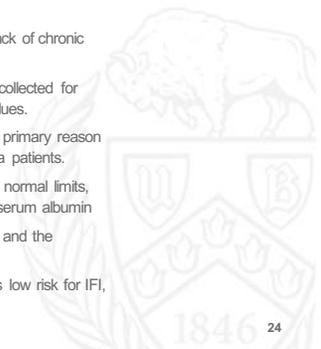
- Examination of ANC levels for the sample show that there is a profound lack of neutropenia across chemotherapy cycles
- Lack of chronic neutropenia decreases risk for contraction of IFI, which may be a primary contributory factor for lack of IFI
- Risk factors that increase risk for IFI include neutropenic depth, and duration. Neutropenia does not occur in the sample overall
- Risk Indexes for Lymphoma patients place lymphoma patients in the low, and intermediate risk category.



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Discussion

- I believe that the reason for the lack of IFI is due to the lack of chronic neutropenia.
- The data collected shows that even the minimum value collected for mean ANC is still within range for normal serum ANC values.
- It cannot be deduced that fluconazole in this study is the primary reason for the lack of fungal infection in this sample of lymphoma patients.
- Serum albumin values also had a mean value within the normal limits, which does not show correlation between infection and serum albumin
- There was no correlation between the age of the patient and the presence of fungal infection.
- Lack of profound neutropenia makes lymphoma patient's low risk for IFI, use of prophylactic fluconazole is recommended.



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Limitations

- Time needed for completion
- Sample size
- Data collected from a single cancer institute
- Lack of a research team
- Most important limitation to this study would be the lack of experience



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Conclusion

- Absence of IFI may be due to lack of profound neutropenia
- Lack of neutropenia places the sample at a low risk for IFI
- Prophylactic recommendations for low risk patient's is the use of fluconazole
- Increased age does not correlate with contraction of IFI
- Mean albumin does not have impact on contraction of IFI
- Continue current practices of prophylactic fluconazole prescribing with frequent lab work monitoring



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Acknowledgements

- Irene, Robert, and Nick Johnson
- Mary Catherine Aungst
- The Lymphoma Team
- Dr. Campbell-Heider, Dr. Bell, Dr. Bruce, and Samantha Hillman



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Thank You!

Questions??



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References

- Pagano, L., Akova, M., Dimopoulos, G., Herbrecht, R., Drgona, L., & Bijljevans, N. (2011). Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. *Journal of Antimicrobial Chemotherapy*, 66(suppl_1), i5-i14. doi:10.1093/jac/dkq437
- Nosari, A. M., Pioltelli, M. L., Riva, M., Marbello, L., Nichelatti, M., Greco, A., . . . Morra, E. (2014). Invasive fungal infections in lymphoproliferative disorders: a monocentric retrospective experience. *Leukemia & Lymphoma*, 55(8), 1844-1848. doi:10.3109/10428194.2013.853299
- Pechlivanoglou, P., Le, H. H., Daenen, S., Snowden, J. A., & Postma, M. J. (2014). Mixed treatment comparison of prophylaxis against invasive fungal infections in neutropenic patients receiving therapy for haematological malignancies: A systematic review. *Journal of Antimicrobial Chemotherapy*, 69(1), 1-11. doi:10.1093/jac/dkt329

References

- Ping, B., Zhu, Y., Gao, Y., Yue, C., & Wu, B. (2013). Second- versus first-generation azoles for antifungal prophylaxis in hematology patients: a systematic review and meta-analysis. *Annals of Hematology*, 92(6), 831-839. doi:10.1007/s00277-013-1693-5
- Dendle, C., Gilbertson, M., Spelman, T., Stuart, R. L., Korman, T. M., Thursky, K., . . . McQuillen, Z. (2017). Infection is an Independent Predictor of Death in Diffuse Large B Cell Lymphoma. *SCIENTIFIC REPORTS*, 7, 1. doi:10.1038/s41598-017-04495-x
- Sun, Y., Huang, H., Chen, J., Li, J., Ma, J., Li, J., . . . Huang, X. (2015). Invasive fungal infection in patients receiving chemotherapy for hematological malignancy: a multicenter, prospective, observational study in China. *Tumor Biology*, 36(2), 757-767. doi:10.1007/s13277-014-2649-7
- Shaw, A. C., Goldstein, D. R., & Montgomery, R. R. (2013). Age-dependent dysregulation of innate immunity. *Nature Reviews Immunology*, 13, 875+.